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April 28, 1992

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Technical Report No. 12

**Enolboration. 3. An Examination of the Effect of Variable Steric Requirements
of R on the Stereoselective Enolboration of Ketones with R_2BCl/Et_3N .
Bis(bicyclo[2.2.2]octyl)chloroborane/Triethylamine - A New Reagent
Which Achieves the Selective Generation of *E* Enolborinates
From Representative Ketones**

by

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Abstract

A smooth, rapid, quantitative and stereoselective enolboration of a variety of ketones to *E* enolborinates is achieved with bis(bicyclo[2.2.2]octyl)chloroborane, Bco₂BCl, a new reagent, in the presence of triethylamine, in simple solvents, such as diethyl ether, hexane, carbon tetrachloride, and methylene chloride. Representative R₂BCl reagents with variable steric requirements have been examined, with 3-pentanone and propiophenone as model ketones, in order to understand the effect of the steric requirements of R in controlling the enolate geometry: (1) *B*-chloro-9-borabicyclo[3.3.1]nonane (B-Cl-9-BBN); (2) di-*n*-butylchloroborane (*n*-Bu₂BCl); (3) bis(*exo*-norbornyl)chloroborane (*exo*-Nrb₂BCl); (4) dicyclooctylchloroborane (Coc₂BCl); (5) disiamylchloroborane (Sia₂BCl); (6) dicyclohexylchloroborane (Chx₂BCl); and (7) bis(bicyclo[2.2.2]octyl)chloroborane (Bco₂BCl). R₂BCl reagents with smaller R groups favor the formation of *Z* enolborinates, whereas those with bulkier R groups favor the formation of *E* enolborinates. The phenyl group also plays a significant role in favoring the *E* enolborinate in the case of propiophenone. The reagent 7, Bco₂BCl, with appropriate steric requirements, provides the best results in generating *E* enolborinates for both the model ketones. Consequently, this new reagent Bco₂BCl, 7, was compared for a variety of ketones with the reagent 6, Chx₂BCl, the best previously available reagent, to give *E* enolborinates. Surprisingly, Bco₂BCl, achieves the *E* enolborinates either exclusively or with a higher selectivity than Chx₂BCl. The enolborinates generated with Bco₂BCl in the presence of triethylamine are highly reactive with aldehydes at temperatures as low as -78 °C. The impressive efficiency of Bco₂BCl in achieving the preferred synthesis of *E* enolborinates, together with its ease of preparation, handling, and greater stability, makes it a valuable reagent for the stereoselective enolboration of ketones. The important effect of variable steric requirements of R in R₂BCl for the stereoselective enolboration of the model ketones and the application of Bco₂BCl to achieve optimum formation of the *E* enolborinates from a variety of ketones are emphasized in this exploratory study.

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Enolboration. 3. An Examination of the Effect of Variable Steric Requirements of R on the Stereoselective Enolboration of Ketones with R_2BCl/Et_3N . Bis(bicyclo[2.2.2]octyl)chloroborane/Triethylamine - A New Reagent Which Achieves the Selective Generation of *E* Enolborinates From Representative Ketones

Herbert C. Brown,* Kumaraperumal Ganesan¹ and Raj K. Dhar¹

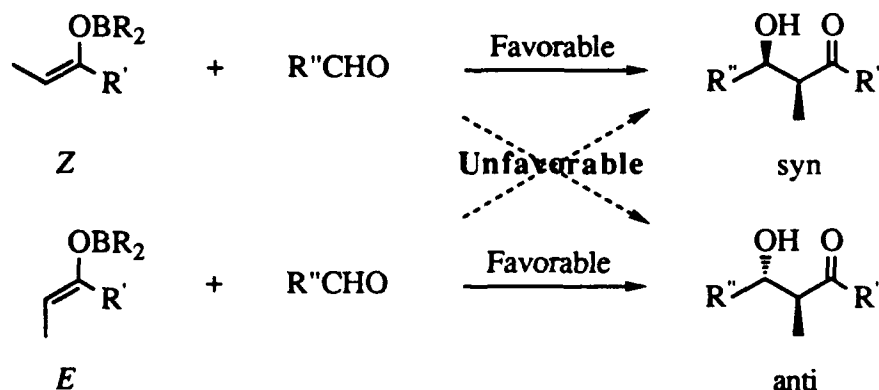
H. C. Brown and R. B. Wetherill Laboratories of Chemistry

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A smooth, rapid, quantitative and stereoselective enolboration of a variety of ketones to *E* enolborinates is achieved with bis(bicyclo[2.2.2]octyl)chloroborane, Bco_2BCl , a new reagent, in the presence of triethylamine, in simple solvents, such as diethyl ether, hexane, carbon tetrachloride, and methylene chloride. Representative R_2BCl reagents with variable steric requirements have been examined, with 3-pentanone and propiophenone as model ketones, in order to understand the effect of the steric requirements of R in controlling the enolate geometry: (1) *B*-chloro-9-borabicyclo[3.3.1]nonane ($B-Cl-9-BBN$); (2) di-*n*-butylchloroborane ($n-Bu_2BCl$); (3) bis(*exo*-norbornyl)chloroborane (*exo*- Nrb_2BCl); (4) dicyclooctylchloroborane (Coc_2BCl); (5) disiamylchloroborane (Sia_2BCl); (6) dicyclohexylchloroborane (Chx_2BCl); and (7) bis(bicyclo[2.2.2]octyl)chloroborane (Bco_2BCl). R_2BCl reagents with smaller R groups favor the formation of *Z* enolborinates, whereas those with bulkier R groups favor the formation of *E* enolborinates. The phenyl group also plays a significant role in favoring the *E* enolborinate in the case of propiophenone. The reagent 7, Bco_2BCl , with appropriate steric requirements, provides the best results in generating *E* enolborinates for both the model ketones. Consequently, this new reagent Bco_2BCl , 7, was compared for a variety of ketones with the reagent 6, Chx_2BCl , the best previously available reagent, to give *E*

enolborinates. Surprisingly, Bco_2BCl , achieves the *E* enolborinates either exclusively or with a higher selectivity than Chx_2BCl . The enolborinates generated with Bco_2BCl in the presence of triethylamine are highly reactive with aldehydes at temperatures as low as -78°C . The impressive efficiency of Bco_2BCl in achieving the preferred synthesis of *E* enolborinates, together with its ease of preparation, handling, and greater stability, makes it a valuable reagent for the stereoselective enolboration of ketones. The important effect of variable steric requirements of R in R_2BCl for the stereoselective enolboration of the model ketones and the application of Bco_2BCl to achieve optimum formation of the *E* enolborinates from a variety of ketones are emphasized in this exploratory study.

Enoborinates are very promising intermediates in organic synthesis.² They are mainly useful for stereocontrolled aldol reactions with high stereoselectivity.^{3-6,13} It has been well demonstrated that *Z* enolborinates give syn aldols and *E* enolborinates give anti aldols stereoselectively^{4,6} (scheme I). Therefore, control of enolate geometry to achieve formation of either *Z* or *E* enolborinates selectively is very important.



Scheme I

Considerable attention has been paid in the past decade to develop simple and efficient methodologies for the generation of enolborinates. This well known methodology involves the

reaction of ketones with a suitable organoboron derivative with a good leaving group, R_2BX , in the presence of a suitable tertiary amine.³ Many of the organoboron reagents developed earlier for this methodology are either difficult to prepare in the pure form or provide only a moderate yield of the desired enolborinates. The lack of control of enolate geometry to provide *E* enolborinates selectively represents another serious limitation of these reagents. The selective generation of *E* enolborinates from ketones had been an unachieved goal of organic chemists.

Generally, both the steric and the electronic effects play important roles in deciding reaction selectivity in chemistry. The steric requirements of substituents, either on the substrate or on boron, play a major role in boron chemistry. Hydroboration is a well studied reaction where such steric influences have been clearly demonstrated.⁸

A recent method to generate enolborinates involves the 1,4-hydroboration of α,β -unsaturated ketones with dialkylboranes.^{9,10} The steric requirements of R in R_2BH decide the mode of addition (1,2 vs 1,4) in this reaction. The less bulky 9-BBN favors a clean 1, 2-addition reaction leading to allyl alcohols,¹¹ whereas bulkier R_2BH reagents, such as Sia_2BH , Chx_2BH , Ipc_2BH and $2-Icr_2BH$, prefer the 1,4-addition pathway, resulting in the synthesis of enolborinates.⁹ The stereochemistry of the resulting enolborinates, the 1,4-addition products, is also controlled by the steric requirements of R in R_2BH . In all of the above cases, the *Z* enolborinates have been obtained exclusively except in the case of 9-BBN, which gives a mixture of both *Z* and *E* enolborinates. The less bulky 9-BBN has also been shown to give either a clean 1,4-addition product¹⁰ or a mixture of both 1,2- and 1,4-addition products^{9b} whereas a clean 1,2-addition reaction, under different experimental conditions, had been observed earlier in our laboratory.¹¹

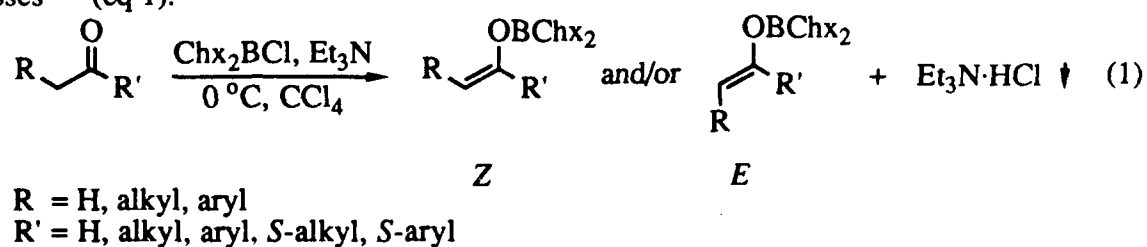
In the enolboration system, Evans had studied the role of steric effects on the boron atom of the enolizing reagent on the enolate geometry.^{4b} In the enolboration of diethyl ketone with R_2BOTf , there was a small increase in the amount of *E* enolborinate formed with a change in the R group from *n*-butyl to cyclopentyl. This result indicates that the bulkier cyclopentyl group favors formation of the *E* enolborinate, as compared to the smaller *n*-butyl group. A better selectivity favoring the *E* enolborinate has also been noted in the enolization of ethyl isopropyl ketone with

Cpn₂BOTf, as compared the results of enolization of the parent diethyl ketone. In this case, however, the larger steric requirements of the ketone substituent, *i*-Pr, may also contribute to this higher stereoselectivity.

Masamune⁵ has achieved the synthesis of either *Z* or *E* enolborinates for selected ketones and thioesters under optimized conditions based on earlier observations. The steric requirements of the substituents on boron reagent must have contributed much to the observed selectivity. He has also reported a high diastereoselectivity for the formation of anti aldols (*E* enolborinates) with his designed reagent, 2,5-dimethylborolanyl triflate.^{12a} In this case also, the selectivity could be attributed to the larger steric requirements of the organic substituents attached to boron.

Meyers has also varied the steric requirements of R in R₂BOTf in the enolboration of oxazolines.^{12b} Even though there were some definite changes observed in the stereoselectivity, no clear cut conclusion as to the effect of R in controlling the enolate geometry was drawn from that study.

One of our research projects involves exploration of new organoboron reagents for achieving control of enolboration and the factors influencing geometry of the enolborinate produced. Our first successful reagent, Chx₂BCl/Et₃N, proved very efficient for the regio- and stereoselective enolboration of various carbonyl compounds^{13a} including a broad range of ketone classes^{13b} (eq 1).



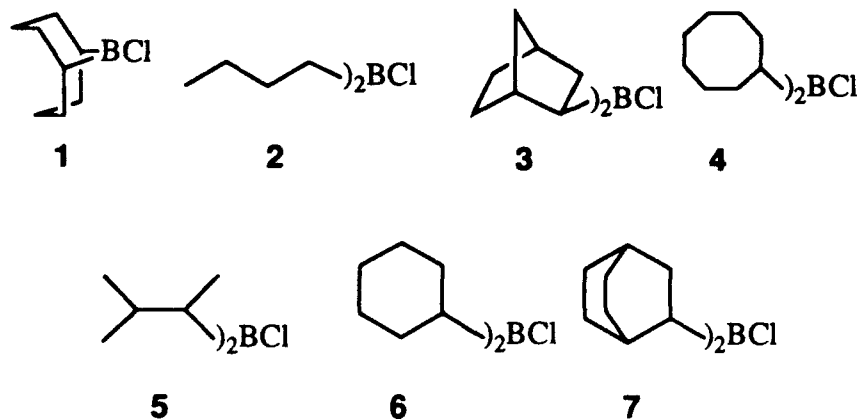
The nomenclature of the enolate (*Z* or *E*) is based on the simplified rule¹⁴ of Evans that for the C-1 enolate substituents R' and OM, the highest priority designation is always assigned to the OM group, independent of the metal. The normal priority designations of substituents at C-2 are maintained. Thus, irrespective of the nature of the R' group (H, alkyl, aryl, *S*-alkyl and *S*-aryl), the enolborinate is designated *Z* when R and OB are cis and *E* when R and OB are trans (eq 1).

This simplified rule has been widely adopted by workers in this field.³⁻⁵ The major advantage of this designation is the simple relationship between the stereochemistry of the enolate and the stereochemistry of the product. In all cases, *Z* enolborinates give syn aldols and *E* enolborinates give anti aldols.

In our earlier communication,^{6b} we mentioned the effect of the steric requirements of the R group in R_2BCl for the preferential generation of *E* enolborinates. Though many reports have pointed out similar effects on enolate geometry, there has been no systematic study designed to achieve an understanding of the factors controlling the stereoselectivity. Therefore, we decided to explore many R_2BCl reagents with variable steric requirements of R in the hope of attaining an understanding of the role of this important steric effect on the enolate geometry, as well as to establish a favorable organoboron reagent for such stereoselective enolborations.

Results and Discussion

More attention has been paid in the present study to the selection of various R_2BCl reagents with varying steric requirements of R, as well as to the selection of the model ketones examined. Based on the ease of preparation, handling, and stability, the following R_2BCl reagents were selected for the present study: (1) *B*-chloro-9-borabicyclo[3.3.1]nonane (B-Cl-9-BBN); (2) di-*n*-butylchloroborane (*n*-Bu₂BCl); (3) bis(*exo*-norbornyl)chloroborane (*exo*-Nrb₂BCl); (4) dicyclooctylchloroborane (Coc₂BCl); (5) disiamylchloroborane (Sia₂BCl); (6) dicyclohexylchloroborane (Chx₂BCl); and (7) bis(bicyclo[2.2.2]octyl)chloroborane (Bco₂BCl).



Ethyl ketones were selected as the best model ketones for the proposed stereochemical study of enolboration. In the present study, therefore, both 3-pentanone, an aliphatic ethyl ketone, and propiophenone, an aromatic ethyl ketone, were selected as model ketones to examine the effect of variable steric requirements of R in the various R_2BCl reagents (1-7) on the geometry of the enolate produced.

Preparation of R_2BCl Reagents. The R_2BCl reagents are readily prepared by the following established methods: (i) hydroboration of the selected alkenes (2 equiv) with borane-methyl sulfide (BMS, 1 equiv) to R_2BH , followed by the controlled addition of anhyd HCl in ether,¹⁵ liberates one molar equivalent of hydrogen, forming R_2BCl ; and (ii) direct hydroboration of the suitable alkenes (2 equiv) with monochloroborane-methyl sulfide (MCBS, 1equiv) to R_2BCl .¹⁶ The second method is especially useful for cases where the hydroboration fails to stop cleanly at the dialkylborane stage. For example, the hydroboration of 1-butene, norbornene, and cyclooctene with BMS proceeds rapidly past the desired R_2BH intermediates to trialkylboranes, R_3B . In such cases, the second method was preferred for the preparation of reagents 2, 3 and 4 from these alkenes. A typical example of the synthesis of Chx_2BCl by both the methods has been described in our earlier paper.^{13a}

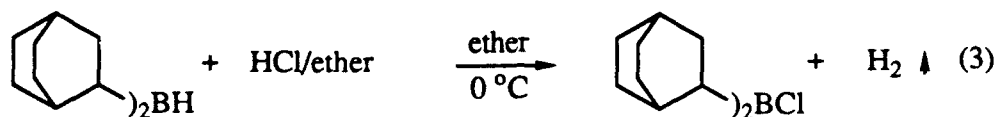
Synthesis of Bco_2BCl (7). The commercially available (Aldrich) monochloroborane-methyl sulfide (MCBS) contains about 5-10% of dichloroborane-methyl sulfide (DCBS) as an impurity. Therefore, the direct hydroboration of bicyclo[2.2.2]oct-2-ene with the commercial MCBS gives only 90-95% of Bco_2BCl along with the impurities, $BcoBCl_2$ and $HBCl_2 \cdot SMe_2$.

Hydroboration of bicyclo[2.2.2]oct-2-ene with borane-methyl sulfide (BMS) has already been shown to give a clean bis(bicyclo[2.2.2]octyl)borane in THF at 25 °C.^{17a} In the present study, we have found that this reaction is rapid and very clean even at 0 °C (eq 2).



The formation of Bco_2BH (δ 19.8 ppm in THF) has also been confirmed by treating it with methanol at 0 °C to the corresponding methyl borinate, Bco_2BOMe (δ 54 ppm in THF). The absence of a peak corresponding to dimethyl boronate, BcoB(OMe)_2 , also confirms the absence of any trace amounts of monoalkylborane, BcoBH_2 in the hydroboration reaction with this olefin.

The conversion of R_2BH to the corresponding R_2BCl using HCl /ether is a simple and well-known method.¹⁵ Therefore, this well established procedure has been used for the synthesis of Bco_2BCl in the present study (eq 3).



The reaction was also followed by measuring the hydrogen gas by a gasimeter and it was quantitative. The Bco_2BCl (δ 80 ppm in ether) was also confirmed by treating it with methanol at 0 °C to the corresponding methyl borinate, Bco_2BOMe (δ 54 ppm in ether). A detailed procedure for the synthesis of Bco_2BCl is given in the experimental section.

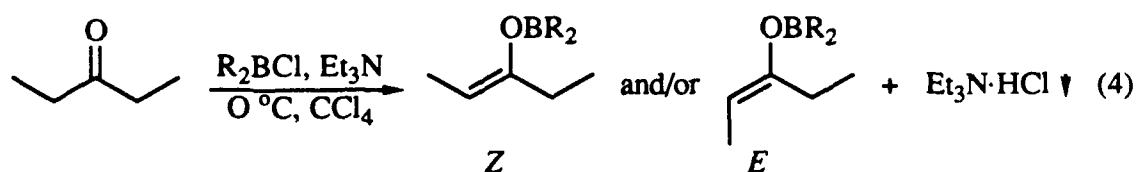
Enolboration. The enolboration experiments were carried out in carbon tetrachloride in cases where it was desirable to record the ^1H NMR spectrum of the reaction mixture. Benzene was added as an internal standard (except in cases where the use of aromatic ketones provided an internal standard) for the quantification of the enolborinates. ^1H NMR spectrum (olefinic proton) was used to determine the extent of enolboration and ^{11}B NMR spectrum (borinate region) was also used to confirm the formation of enolborinates. This is a new established technique which we have been using for quantification of enolborinates.^{6b,13} Enolization could also be carried out successfully in other organic solvents, such as CH_2Cl_2 , diethyl ether, and hexane. Wherever aldolization was to be performed on the enolborinate, the corresponding enolization was carried out either in diethyl ether or in hexane. The rate of the enolboration reaction could be readily followed by observing the precipitation of $\text{Et}_3\text{N}\cdot\text{HCl}$ from the reaction mixture.

Effect of the Steric Requirements of R in R₂BCl on the Enolate Geometry.

A systematic study has been undertaken to examine the effect of variable steric requirements of the substituent R in the various R₂BCl reagents (1-7) in controlling the stereochemistry of the enolboration for the two model ketones, 3-pentanone and propiophenone.

Stereoselective Enolboration of 3-Pentanone. Generation of the kinetic *E* enolborinate from 3-pentanone has been a great challenge to organic chemists. The first achievement was the discovery in our laboratory of the enolization of 3-pentanone by Chx₂BCl/Et₃N to give 79% *E* enolborinate.^{6b} Since the original communication, this reagent has been utilized by a number of research workers to achieve the preferential synthesis of *E* enolborinates. For example, the value of Chx₂BCl/Et₃N has been well demonstrated by Ian Paterson with the anti selective and quantitative aldolization of α -chiral ethyl and methyl ketones with various aldehydes, such as aliphatic, α,β -unsaturated and aromatic.^{17b}

In our attempt to understand the effect of the steric requirements of the alkyl groups of the boron reagent on the enolate geometry, we were pleasantly surprised with a bonus that a new reagent, bis(bicyclo[2.2.2]octyl)chloroborane, Bco₂BCl, achieves the synthesis of the *E* enolborinate predominantly (>97%) from 3-pentanone. The results of the enolboration of 3-pentanone with the various R₂BCl reagents (1-7) in the presence of triethylamine (eq 4) are summarized in Table I.



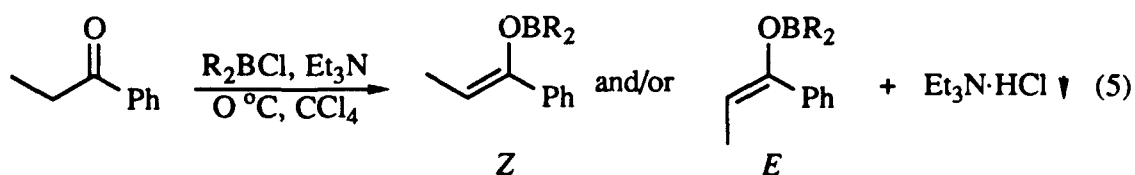
From the results in Table I, it is evident that the steric requirements of R in R₂BCl exert a major influence in controlling the enolate geometry in the enolization process. In the case of the relatively smaller reagent B-Cl-9-BBN, 1, the *Z* enolborinate is obtained exclusively from 3-pentanone, whereas in the case of the bulkier Bco₂BCl, 7, essentially the isomeric *E* enolborinate is produced exclusively. As the steric requirements of R increase from the reagent 1 to 7, the

selectivity toward the formation of the *E* enolborinate also increases. It can be safely concluded that the small R_2BCl reagents favor formation of the *Z* enolate and the bulky R_2BCl reagents favor formation of the *E* enolate. It is now possible to achieve the synthesis of either *Z* or *E* enolborinate selectively from 3-pentanone merely by a careful selection of the boron reagent. Except for the reagent 5, all other R_2BCl reagents studied provide essentially quantitative yields of the enolborinates. It is interesting to note that the reagent couples 1 and 2, and, 4 and 5, give essentially individual identical mixtures of *Z* and *E* enolborinates for each reagent in the couple.

It is important to note that R_2BCl reagents with even greater steric requirements, such as bis(2,5-dimethylcyclohexyl)chloroborane, 2,5-Me₂Chx₂BCl, fail to enolize 3-pentanone quantitatively.^{13a} Apparently, there is a choice between reactivity and selectivity as the steric requirements of R in R_2BCl increase. Fortunately, the reagent 7, Boc₂BCl, with appropriate steric requirements, is both reactive and selective.

Stereoselective Enolboration of Propiophenone. Propiophenone, a widely studied ketone, was selected as the model aromatic ethyl ketone. The earlier literature reveal that enolboration of propiophenone gives the *Z* enolborinate predominantly. The highest conversion to the *E* enolborinate reported^{4b} for the enolboration of propiophenone with R_2BOTf is only 3%. Consequently, it was gratifying to observe that our reagent, Chx₂BCl/Et₃N, converts propiophenone almost exclusively to the *E* enolborinate.^{6b,13}

The results of the enolboration of propiophenone (eq 5) with the various R_2BCl reagents are also included in Table I.

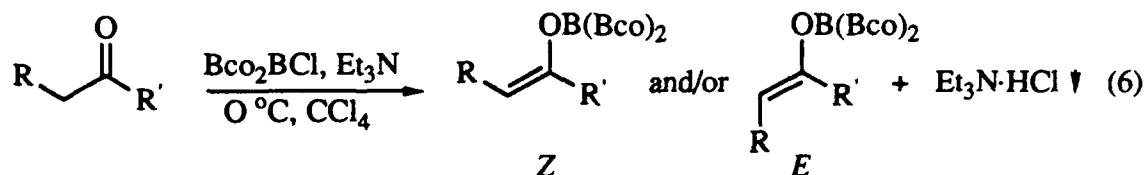


The results obtained in the case of propiophenone also support our earlier conclusion on the influence of the steric effect on the control of the enolate geometry. As the steric requirements of R in R_2BCl increase from the small B-Cl-9-BBN to the bulky Bco₂BCl, the selectivity favoring

formation of the *E* enolborinate also increases. An unexpected development from this study is the observation that many reagents, 3-7, convert propiophenone to *E* enolborinate either exclusively or predominantly. A careful comparison of the results in Table I obtained for both 3-pentanone and propiophenone with the same reagent suggests that the phenyl group must also play a vital role in favoring formation of the *E* enolate. Similar effects of the phenyl group has also been observed in the enolboration of esters and amides.¹⁸ The similarity observed in the distribution of *Z* and *E* enolborinates with the reagent couples 1 and 2, and, 4 and 5, in the case of 3-pentanone is also evident for propiophenone.

Comparison of Bco_2BCl with Chx_2BCl . From the results in Table I, it is apparent that only Bco_2BCl possesses the optimum steric requirements to convert both model ketones essentially, exclusively into their *E* enolborinates. Earlier it had been established that $\text{Chx}_2\text{BCl}/\text{Et}_3\text{N}$ achieves the conversion of the various ethyl ketones, such as ethyl isopropyl ketone, ethyl cyclohexyl ketone, and ethyl *tert*-butyl ketone, into the *E* enolborinates almost exclusively.^{6b,13} However, $\text{Chx}_2\text{BCl}/\text{Et}_3\text{N}$ was less successful in converting diethyl ketone, ethyl isobutyl ketone, di-*n*-propyl ketone, and di-*n*-butyl ketone into their *E* enolborinates. The *E* enolborinates are formed predominantly, but not exclusively. However, the new reagent, Bco_2BCl , achieves the conversion of all these ketones almost completely into the desired *E* enolborinates. The exclusive formation of the *E* enolates from all these ketones has not previously been accomplished from either boron or non-boron reagents. Therefore, to obtain a true comparison of the efficiency of the new reagent, $\text{Bco}_2\text{BCl}/\text{Et}_3\text{N}$, with the earlier reagent, $\text{Chx}_2\text{BCl}/\text{Et}_3\text{N}$, these ketones were treated with these two reagents under rigorously controlled condition.

The results in Table II clearly show that the new reagent, Bco_2BCl , provides *E* enolborinates with a better selectivity than Chx_2BCl for the eight ketones studied (eq 6).



R = Me, Et, *n*-Pr

R' = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, Chx, Ph

The reaction is rapid and is conveniently followed by the concurrent formation and precipitation of triethylammonium chloride, and is essentially quantitative except for the sterically hindered ethyl *tert*-butyl ketone. A similar slow enolboration has also been reported for this ketone in the literature^{4b} with *n*-Bu₂BOTf/*i*-Pr₂EtN. The yields obtained with the new reagent are also comparable with Chx₂BCl/Et₃N. These yields are based on the isolation and weight of the solid Et₃N·HCl, by the reaction of the enolborinate with a measured amount of benzaldehyde, or by ¹H NMR examination of the aldol produced.

This comparative study also gives further evidence for our earlier important conclusion that the smaller R₂BCl favors *Z* enolate formation and the bulky R₂BCl favors *E* enolate formation. This is also the first study of the stereoselective enolboration of higher ketones, such as di-*n*-propyl and di-*n*-butyl ketones. Even in these cases, the new reagent achieves the exclusive formation of the *E* enolborinates.

Determination of the Enolate Geometry. The direct determination of the *Z/E* ratio by ¹H NMR is extremely difficult, since the olefinic protons of both *Z* and *E* enolborinates exhibit essentially identical chemical shift. Conversion of these enolborinates into the corresponding enol ethers followed by the GC analysis has been one of the methods to determine this ratio.^{4b} However, possible isomerization during these processes led us to prefer the aldol procedure.^{6b,13} As mentioned earlier, aldol reactions of enolborinates are highly stereoselective with *Z* and *E* enolborinates giving syn and anti aldols respectively (scheme I). An indirect method was, therefore, established and used to determine this ratio from the syn/anti ratio of the corresponding aldol products formed by the treatment with benzaldehyde. The chemical shift and the coupling constant values of the carbinol protons (benzylic in this case) of these syn and anti aldols are different.

Consequently, the crude aldol reaction mixture (after the standardized workup) was analyzed as such by ^1H NMR to get this ratio precisely. This is an established technique^{6b,13} to determine the *Z/E* ratio of the enolborinates when the direct determination by ^1H NMR is difficult. The required ^1H NMR data for both syn and anti aldols are given in Table III.

In the case of propiophenone, as reported earlier for other aromatic ketones,^{6b,13} it is possible to determine the *Z/E* ratio directly by ^1H NMR examination of the reaction mixture, since the *Z* and *E* enolborinates exhibit different chemical shifts. The olefinic proton of the *Z* enolborinate appears at δ 5.5 ppm (*q*, $J = 7.4$ Hz) and that of the *E* enolborinate appears at δ 5.1 ppm (*q*, $J = 7.4$ Hz). However, in all the cases, the syn/anti ratio was also determined for the aldol products obtained by treating the enolborinates of propiophenone with benzaldehyde. The syn/anti ratio of the aldols corresponds closely to the directly determined *Z/E* ratio of the enolborinates, further supporting the high stereoselectivity of enolborinates.

In a number of cases, the enolization produced essentially one of a pair of isomeric enolates. Since it is difficult to see very small amounts of the minor component against the background, we have indicated the products to be <3% for the minor isomer and >97% for the major isomer, although the spectrum itself shows only the major isomer.^{13b}

Conclusions

This is the first systematic and detailed study of the effect of variable steric requirements of *R* in R_2BCl on the stereoselective enolboration of ketones. The present study using two model ketones, diethyl ketone, an aliphatic ethyl ketone, and propiophenone, an aromatic ethyl ketone, reveals that the smaller R_2BCl reagents favor formation of the *Z* enolborinates, while the bulkier R_2BCl reagents favor formation of the *E* enolborinates. In the case of propiophenone, the significant effect of the phenyl group favoring formation of the *E* enolborinate has also been observed. The achievement of five R_2BCl reagents, 3-7, which convert propiophenone to its *E* enolborinate essentially exclusively, is also another bonus from this study. Surprisingly, Bco_2BCl , a new reagent with the appropriate steric requirements, is the only reagent which achieves formation of the *E* enolborinates exclusively from the model ketones. A true comparison

of this new reagent with Chx_2BCl , our standard organoboron reagent, in the stereoselective enolboration of eight different ketones, reveals that Bco_2BCl is more selective than Chx_2BCl in achieving the *E* enolborinates. We suggest application of $\text{Bco}_2\text{BCl}/\text{Et}_3\text{N}$ to those ketones which fail to form the *E* enolborinates selectively with $\text{Chx}_2\text{BCl}/\text{Et}_3\text{N}$, since the synthesis of the latter reagent is comparatively easy and the olefin used for the synthesis is much less expensive. This systematic study also provides information that can be helpful in designing new reagents for stereoselective enolboration. Finally, the visual observation of the formation of $\text{Et}_3\text{N}\cdot\text{HCl}$ as a white precipitate as the enolboration progresses is an added advantage for these reagents in providing a convenient visual guide to the course of the reaction. The new reagent, Bco_2BCl , which favors so strongly the stereoselective formation of *E* enolborinates, definitely fills a long standing vacuum in this area.

Experimental Section

Materials. All glassware was thoroughly dried in an air oven, cooled and assembled under nitrogen for the experiments. Degassed, anhyd solvents, CH_2Cl_2 , CCl_4 , and hexane, were used. THF was freshly distilled from sodium benzophenone ketyl. Et_3N was distilled over CaH_2 . All alkenes and ketones, except for ethyl *tert*-butyl ketone, were commercial products of the highest purity available. Whenever necessary, the commercial samples of liquid alkenes were purified by distillation over a small quantity of LiAlH_4 . Borane-methyl sulfide (BMS) and monochloroborane-methyl sulfide (MCBS) reagents were purchased from Aldrich and used as such for the reaction.

Synthesis of R_2BCl reagents. The synthesis of Chx_2BCl as a general procedure for the various R_2BCl reagents (except for 2 and 7) has been described in our earlier paper.^{13a} The synthesis of *n*- Bu_2BCl , 2, has also been reported elsewhere.^{16c} The experimental procedure for the synthesis of Bco_2BCl , 7, a new reagent, is described in this section. The special experimental techniques used in handling air- and moisture-sensitive compounds have been described elsewhere.^{8a} All of the following experiments were conducted under an inert atmosphere (N_2).

Synthesis of Bco_2BCl . A 500 mL round-bottom flask fitted with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler is charged with THF (150 mL) [other solvents, such as CH_2Cl_2 , and diethyl ether are not as satisfactory] and bicyclo-[2.2.2]oct-2-ene (20 g, 185 mmol). The flask is cooled in an ice bath and borane-methyl sulfide (BMS, 9.25 mL, 10.0 M, 92.5 mmol), is added slowly with constant stirring. The reaction is continued at 0 °C and the formation of Bco_2BH is complete within 1 h (^{11}B NMR, δ 19.8 ppm in THF). Then both THF and Me_2S are removed by a water aspirator (15-20 mm). The viscous Bco_2BH is redissolved in ether (100 mL) and anhyd HCl in ether (37.0 mL, 2.50 M, 92.5 mmol) is added slowly to this solution at 0 °C. Hydrogen is rapidly evolved and should be safely vented. In a test reaction, the hydrogen gas was estimated by a gasimeter and was quantitative. Stirring is continued at 0 °C for an additional 1-2 h. The ^{11}B NMR analysis of the resulting colorless solution shows the clean formation of Bco_2BCl (δ 80 ppm in ether). The solvent ether is removed by a water aspirator (15-20 mm) and the resulting Bco_2BCl (>98% pure based on the ^{11}B NMR), a colorless liquid, is used as such, since it decomposes on attempted distillation at 0.1 mm.

Synthesis of Ketones. Ethyl *tert*-butyl ketone was prepared directly by the chromic acid two phase (ether-water) oxidation¹⁹ of the corresponding alcohol (commercially available). Distillation provided >99% GC pure ketone and ^1H NMR spectrum confirmed the structure.

Spectra. ^1H NMR spectra were recorded on T-60, and 300-MHz instruments. ^{11}B NMR spectra were recorded on FT-80A and 300-MHz instruments. The chemical shift values are in δ (ppm) relative to $\text{BF}_3\cdot\text{OEt}_2$.

General Procedure for the Enolboration of Ketones With $\text{R}_2\text{BCl}/\text{Et}_3\text{N}$. A simple and general procedure for the enolization of ketones is described as follows. To a stirred solution of R_2BCl (5.15 mmol), and Et_3N (0.72 mL, 5.16 mmol) in CCl_4 (17 mL), cooled at 0 °C (except for ethyl *tert*-butyl ketone which requires 25 °C) under a N_2 atmosphere, the ketone (5.0 mmol) is added dropwise. The enolborinate is generated instantaneously with concurrent formation and precipitation of $\text{Et}_3\text{N}\cdot\text{HCl}$. An internal standard, benzene (0.50 mmol), is added for quantification of the enolborinate by ^1H NMR analysis, except in the case of propiophenone,

where the aromatic ring is used as the internal standard. The molarity is adjusted to 0.2-0.3 M. The reaction mixture is stirred for 1 h and transferred into a centrifuge vial using a double-ended needle (18 gauge). Centrifugation results in the separation of the enolborinate solution from the precipitated $\text{Et}_3\text{N}\cdot\text{HCl}$. In representative cases, the solid $\text{Et}_3\text{N}\cdot\text{HCl}$ has been collected, washed, dried, and weighed. Essentially quantitative yields are obtained. The enolborinate solution is then transferred into an NMR tube using a double-ended needle. The ^1H NMR analysis gives the extent of enolboration and the ^{11}B NMR (borinate region, usually broad, around 50-56 ppm) also confirms the formation of enolborinates. The ^1H NMR data of the olefinic protons of the enolborinates are given in our earlier papers.¹³

General Procedure for the Aldolization with Benzaldehyde. To a solution of enolborinate in diethyl ether (or hexane), generated under a N_2 atmosphere from 5.0 mmol of the ketone using $\text{R}_2\text{BCl}/\text{Et}_3\text{N}$ as described above, benzaldehyde (5.0 mmol) is added dropwise at -78°C . The reaction mixture is stirred for 2-3 h and then allowed to warm up overnight slowly to attain room temperature. The absence of residual benzaldehyde confirms the essentially quantitative formation of enolborinate, as indicated by ^1H NMR analysis. Then 10 mL of methanol is added to dissolve the precipitate ($\text{Et}_3\text{N}\cdot\text{HCl}$) and 1.7 mL of H_2O_2 (30%) is added at 0°C . The resulting mixture is stirred at 0°C for 30 min and then at 25°C for 5-6 h. The solvent and methanol are then removed by a water aspirator (15-20 mm) and the reaction mixture is extracted with ether, washed with dilute HCl and water, and then dried over anhyd Na_2SO_4 . The solvent is removed and the products are analyzed as such by ^1H NMR (in CDCl_3) to determine the syn/anti ratio.

Supplementary Material Available: ^1H NMR spectra (8 pages) of the benzaldehyde aldols of the various ethyl ketones, EtCOR , with $\text{R} = \text{Et}$ (anti), Ph (anti), *i*-Pr (anti), Chx (anti), *t*-Bu (anti), *i*-Bu (mixture), and other ketones $n\text{-Pr}_2\text{CO}$ (anti), and $n\text{-Bu}_2\text{CO}$ (anti). Ordering information is given on any current masthead page.

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Table I. Effect of the Steric Requirements of R in R₂BCl on Enolate Geometry in the Enolboration of 3-Pentanone and Propiophenone with Various R₂BCl/Et₃Na.^{a,b}

| R ₂ BCl | 3-pentanone ^c (%) | | | propiophenone ^{d,e} (%) | | |
|--------------------|------------------------------|----|----------------------|----------------------------------|-----|----------------------|
| | Z | E | yield ^{f,g} | Z | E | yield ^{f,g} |
| 1 | >97 | <3 | 95 | 52 | 48 | 91 |
| 2 | 97 | 3 | 94 | 51 | 49 | 90 |
| 3 | 40 | 60 | 96 | 4 | 96 | 90 |
| 4 | 30 | 70 | 96 | 3 | 97 | 92 |
| 5 ^h | 30 | 70 | 60 | 3 | 97 | 57 |
| 6 | 21 | 79 | 95 | <3 | >97 | 92 |
| 7 | 3 | 97 | 90 | <3 | >97 | 90 |

^aReactions were carried out in CCl₄ at 0 °C unless otherwise stated.

^bIn cases where the spectrum shows only one major isomer, we have indicated the minor isomer to be <3% since such small peaks may be lost in the background. ^cZ/E ratio was determined based on the syn/anti ratio of their corresponding benzaldehyde aldol products. ^dZ/E ratio was directly determined by ¹H NMR. ^eZ/E ratio was also confirmed by the syn/anti ratio of the corresponding aldols with benzaldehyde. ^fDetermined by ¹H NMR. ^gThe yields were also confirmed by collecting and weighing the precipitated Et₃N·HCl. ^hReactions at 25 °C.

**Table II. Comparison of Bco₂BCl/Et₃N with Chx₂BCl/Et₃N
for the Stereoselective Enolboration of Various Ketones^{a,b}**

| RCOR' | | Chx ₂ BCl ^c (%) | | | Bco ₂ BCl ^c (%) | | |
|--------------|---------------------------|---------------------------------------|-----|--------------------|---------------------------------------|-----|--------------------|
| R | R' | Z | E | yield ^d | Z | E | yield ^d |
| Et | <i>i</i> -Pr | <3 | >97 | 95 | <3 | >97 | 94 |
| Et | Chx | <3 | >97 | 96 | <3 | >97 | 95 |
| Et | <i>t</i> -Bu ^e | <3 | >97 | 60 | <3 | >97 | 55 |
| Et | Ph | <3 | >97 | 92 | <3 | >97 | 90 |
| Et | Et | 21 | 79 | 95 | 3 | 97 | 90 |
| Et | <i>i</i> -Bu | 17 | 83 | 96 | 11 | 89 | 94 |
| <i>n</i> -Pr | <i>n</i> -Pr | 20 | 80 | 95 | <3 | >97 | 94 |
| <i>n</i> -Bu | <i>n</i> -Bu | 29 | 71 | 95 | <3 | >97 | 93 |

^aReactions were carried out in CCl₄ at 0 °C unless otherwise stated.

^bRefer to footnote (b) under Table I. ^cZ/E ratio was determined based on the syn/anti ratio of their corresponding benzaldehyde aldol products.

^dRefer to footnotes (f and g) under Table I. ^eReaction at 25 °C.

**Table III. ^1H NMR Data of the Carbinol
Protons of the Syn and Anti Aldols**

| RCOR' | | ^1H NMR ^a (δ ppm) | |
|--------------|--------------|---|-------------------------|
| R | R' | syn | anti |
| Et | <i>i</i> -Pr | 4.63 (d, $J = 6.0$ Hz) | 4.43 (d, $J = 8.6$ Hz) |
| Et | Chx | 4.81 (d, $J = 5.0$ Hz) | 4.63 (d, $J = 8.0$ Hz), |
| Et | <i>t</i> -Bu | 4.80 (d, $J = 4.0$ Hz) | 4.68 (d, $J = 8.0$ Hz) |
| Et | Ph | 5.08 (d, $J = 4.0$ Hz) | 4.88 (d, $J = 8.0$ Hz) |
| Et | Et | 5.01 (d, $J = 4.4$ Hz) | 4.72 (d, $J = 8.4$ Hz) |
| Et | <i>i</i> -Bu | 5.00 (d, $J = 4.5$ Hz) | 4.71 (d, $J = 8.3$ Hz) |
| <i>n</i> -Pr | <i>n</i> -Pr | 4.80 (d, $J = 6.2$ Hz) | 4.75 (d, $J = 7.6$ Hz) |
| <i>n</i> -Bu | <i>n</i> -Bu | 4.79 (d, $J = 6.0$ Hz) | 4.74 (d, $J = 7.1$ Hz) |

^aCorresponds to the benzylic proton of the benzaldehyde aldol products.